REMARKS

The Office Action mailed March 26, 2002 has been received and carefully reviewed. After entry of the present amendment, claims 1-11, 18-20 and 22-27 are pending in the application. Claims 1, 20, 23 and 24 have been amended. New claims 25-27 were introduced. No new matter has been added.

Support for the new claims reciting a sensitive period can be found in the specification at least at page 5, lines 28-33. Support for claims directed to human and rat fetal cells derived from embryos during specific sensitive periods can be found in the specification at least at page 6, lines 1-3.

Favorable reconsideration and withdrawal of the rejections of the claims is respectfully requested in light of the amendments and comments presented herein.

Rejection of Claims Under § 112, First Paragraph

In the Office Action, the rejection of claims 14-15 for lack of enablement was maintained. The rejection of claims 1-11 for scope of enablement was maintained. In addition, claims 20-23 were newly rejected for lack of enablement. For the reasons discussed below, these rejections are traversed.

The Rejection of Claims 14-15

In the prior Office Action mailed July 31, 2001, claims 14-15 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Applicants traversed the rejection of these claims in a Response mailed December 28, 2001. In the presently pending Office Action, the Examiner argues that Applicant's arguments are not persuasive and maintains the rejection. Applicants respectfully disagree with the Examiner's assertions. Nonetheless, in order to further prosecution of the application, these claims have been cancelled in the present amendment. Applicants reserve the right to pursue the subject matter of these claims in a continuation application.

Maintained Rejection of Claims 1-11

With regard to the rejection of claims 1-11, the Examiner argues that "the claims are only enabled for CNS precursor cells obtained from rats or humans." Thus, the

Examiner has acknowledged that at least new claims 26 and 27, reciting human fetal cells and rat fetal cells, respectively, are fully enabled. For the following reasons, Applicants also respectfully assert that amended claim 1 and claims 2-11 depending therefrom, in addition to new claim 25, are fully enabled by the specification as filed.

As amended, claim 1 recites "wherein said precursor cells comprise fetal central nervous system cells." It is respectfully asserted that the specification enables the full scope of the claims, as it provides considerable guidance to one of skill in the art regarding fetal CNS precursor cells, including a functional description, where they can be found, and when they should be harvested.

At least at page 5 of the specification, a "precursor cell" is defined as "a cell that is capable of differentiating to form a specific cell type, but does not yet express proteins associated with a specific cell type." It is respectfully asserted that numerous assays useful in determining whether a cell expresses identified proteins are well known. Thus, in light of the acknowledged high level of skill in the art, it is within the skilled person's capability to determine whether a cell is a precursor cell by determining whether it expresses the proteins of the corresponding differentiated cell type. For example, the specification notes that dopaminergic neurons not only secrete dopamine as a neurotransmitter, but also express high levels of tyrosine hydroxylase, which is readily assayed. See page 8, lines 7-10.

Moreover, contrary to the assertion in the office action, the specification does define the "sensitive period" during fetal development during which the CNS precursors should be harvested: "the period during which precursor cells can be obtained that produce a very large number of a specific differentiated cell type." See page 5, lines 30-31. It is respectfully asserted that those of skill in the art could readily ascertain, from known neural development patterns, when fetal CNS cells begin to differentiate into their respective cell types. In addition, as noted by the Examiner, the specification provides sensitive periods for both rats and humans. It is respectfully asserted, based on the foregoing, that sensitive periods for other species are known or readily identifiable.

The specification also describes several locations for obtaining precursor cells to make specific differentiated cell types according to the method of the invention. Three examples include the midbrain/hindbrain junction for dopaminergic cells, the basal

forebrain and spinal cord for cholinergic cells, and the nucleus raphe for serotonergic cells. See page 7, lines 31-35.

Thus, it is respectfully asserted that the specification provides ample direction to one of skill in the art such that they would readily be able to obtain the starting materials for the method of the claims, and would therefore be able to make and use the invention without undue experimentation.

For at least the foregoing reasons, it is asserted that the claims are fully enabled. Withdrawal of the rejection and notification to that effect is respectfully requested.

Rejection of Claims 20-23

In the Office Action, claims 20-23, previously drawn to a method of treating a patient for a neurological disorder were rejected for lack of enablement. Applicants respectfully traverse the rejection. However, to further prosecution of the application, claim 20 has been amended and is now drawn to a method of treating a patient for Parkinson's disease. Consequently, claim 21, which was incorporated by the amendment to claim 20, was cancelled. Applicants assert that claims 20, 22 and 23 as amended are fully supported by the specification as filed.

As argued previously, cell replacement therapies, although relatively new, have demonstrated clinical successes. The instant specification teaches that by 1996, fetal nigral cells, which are included in the definition of precursor cells, had been transplanted with clinical success and good graft survival and innervation in over 200 late stage Parkinson's patients worldwide. See page 1. Bjorklund et al. (2000) (included with previous response) teaches that "fetal neural transplantation is well justified in patients with PD. . . because it has already been shown to work in relevant rodent and primate models, and because its efficacy. . .can be attributed to specific biological mechanisms." See p.537, cols. 1-2.

Citing Clarkson et al. (1999) and Olanow et al. (1996), the Examiner argues that "an obstacle to success in neural cell transplantation is graft survival." However, the Bjorklund et al. (2000) reference cited by the Examiner also notes that that some of the inventors of the instant application previously showed that *in vitro* expanded precursors can survive transplantation. See page 12. Although an overall 95% loss of cells was

observed, it is respectfully asserted that this low rate of cell survival is recognized and overcome in the present application. The Examiner is respectfully directed to page 12 of the instant specification which provides ample guidance to one of skill in the art where it is taught that about 100-500 aggregates should be transplanted per side to achieve successful therapy. See page 12, lines 23-30. As demonstrated in the working examples using rat models, graft survival and functional integration is achieved by the claimed methods. See pages 26-27, Example 5. In particular, the Examiner is directed to pages 27-28 where immunohistochemical data is presented, demonstrating viable grafts exhibiting TH-immunoreactivity 80-101 days after transplantation.

As argued previously and as recognized by the Examiner, the rat model used in the examples of the specification is a well-established model for Parkinson's disease that is known to "have good predictive value with respect to effects of therapeutic interventions on symptoms in PD patients." See Bjorklund (2000), page 537, column 3. It is asserted that concerns regarding mouse ES cells and primate models as they apply to other neurodegenerative disorders are not applicable to the instant claims, which as amended, are drawn to a treatment of Parkinson's disease.

It is asserted therefore, that amended claim 20 and claims 22 and 23 depending therefrom are amply supported and enabled by the specification. Withdrawal of the rejection and notification to that effect is requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Maintained rejection of claims 14-15

As noted, claims 14 and 15 have been cancelled without prejudice in the present amendment. Therefore, the rejection based on § 112, second paragraph is rendered moot. Withdrawal is respectfully requested.

Rejection of claims 20-24

Claim 20 was rejected as indefinite for lacking a method step that relates back to the preamble. It is respectfully asserted that the amendment of Claim 20 incorporating a relation back overcomes the rejection. Notification to that effect is earnestly solicited.

Claim 23 was rejected as indefinite for reciting "a therapeutically offensive amount." This typographical error was corrected by amendments made herein.

Claim 24 was rejected for reciting "an assay for a substance" without reciting a purpose. The Examiner is thanked for the suggestion to incorporate language similar to that taught in the specification. The suggested changes have been incorporated.

It is believed that the present amendments to the claims overcome the pending indefiniteness rejections. Notification to that effect is earnestly solicited.

Rejections Under 35 U.S.C. § 102(b)

In the Office Action, claims 1, 3 and 7-11 are rejected under 35 U.S.C. § 102(b) as anticipated by (or in the alternative, obvious over) Buc-Caron. Applicants traverse these rejections.

The Examiner argues that Buc-Caron teaches a method of generating dopaminergic neuron cells by proliferating and differentiating CNS precursor cells. The Examiner assumes that Buc-Caron's method, which results in a heterogenous culture, includes cholinergic neuronal cells and serotonergic cells. The Examiner also assumes that Buc-Caron's use of OPTI-MEM during differentiation supplies ascorbic acid and, citing Eldridge, argues that ascorbic acid is known to play a role in stimulating differentiation of precursor cells.

First, it is respectfully asserted that the Examiner has assumed too much. It is the Examiner's burden to factually support a prima facie conclusion of obviousness. MPEP 2142. Furthermore, "when a rejection is based on facts within the personal knowledge of the Examiner, the data should be stated as specifically as possible, and the facts must be supported, when called for by the applicant, by an affidavit from the examiner." MPEP 2144.03. It is respectfully asserted that the Examiner's above-noted assumptions do not meet the burden of factually supporting the rejection. If the Examiner is basing these assumptions on personal knowledge, an affidavit is respectfully requested.

Second, it is respectfully asserted that all limitations of the rejected claims are not taught or suggested by Buc-Caron and/or Eldridge. The step of "incubating precursor cells in an incubation vessel which contains differentiation medium in a manner effective to form a reaggregation of differentiated dopaminergic neuron cells that is not adhered to

any surface of the incubation vessel, wherein the differentiation medium includes ascorbic acid" is not taught or suggested. In contrast to the instant claims, Buc-Caron does not suggest any differentiation steps following the proliferation steps. The method of Buc-Caron also does not result in a cell culture comprising differentiated dopaminergic cells, as required by the instant claims.

Eldridge et al. teaches that ascorbic acid promotes Schwann cell myelin formation by enabling the Schwann cell to assemble a basal lamina, which is required for complete differentiation. This reference neither teaches nor suggests the desirability of using ascorbic acid to induce the differentiation of proliferated neuronal precursor cells to dopaminergic cells. It is respectfully asserted, therefore, that the Eldridge et al. reference does not cure the deficiencies of Buc-Caron.

For these reasons, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

In the Office Action, claims 1-4 and 7-11 are rejected under 35 U.S.C. § 103(a) over the combination of Buc-Caron and Studer (Current Protocols in Neuroscience). These rejections are traversed.

"To establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP 2143.03. For the reasons noted above, Buc-Caron does not teach or suggest all limitations of the rejected claims. Studer does not supplement Buc-Caron so as to cure the deficiencies.

The Studer method is described in the instant specification (see page 6, lines 4-5) as the preferred method of trituration. Although the reference describes the use of roller tubes and the number of cells to culture in the proliferation step, it does not teach or suggest the differentiation step of the instant claims. As is the case with Buc-Caron, there is no mention of the use of ascorbic acid in the differentiation step or the production of dopaminergic cells.

Thus, it is respectfully asserted that the instant claims are patentable over the cited references. Withdrawal of the rejection and notification to that effect is earnestly solicited.

Allowed Claims

Applicants thank the Examiner for notification of the allowance of claims 18 and 19.

Summary

In summary, Applicants believe that each of claims 1-11, 18-20 and 22-27 are in condition for allowance. Further and favorable action in the form of a Notice of Allowance is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below, if the Examiner believes that doing so will expedite prosecution of this patent application.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332.5300

Date: 7/26/02

Wendy M. Seffrood

Name: Wendy M. Seffrood
Reg. No.: P-52,205

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 14, 15 and 21 were cancelled in the present amendment. Claims 1, 20, 23 and 24 were amended as follows.

1. (TWICE AMENDED) A method of generating a cell culture comprising dopaminergic neuron cells, said method comprising:

a. proliferating precursor cells, said step of proliferating comprising:

i. incubating a suspension of said precursor cells in a proliferating medium which includes basic fibroblast growth factor (bFGF) to form proliferated precursor cells; and

b. differentiating said precursor cells, said step of differentiating comprising:

i. incubating said precursor cells in an incubation vessel which contains differentiation medium in a manner effective to form a reaggregation of differentiated dopaminergic neuron cells that is not adhered to any surface of the incubation vessel, wherein the differentiation medium includes ascorbic acid;

wherein said precursor cells comprise [CNS stem cells] fetal central nervous system cells.

20. (AMENDED) A method of treating a patient [for a neurological disorder] for Parkinson's disease, said method comprising administering cells produced according to the method of claim 1 to the patient to treat the patient for Parkinson's disease.

23. (AMENDED) The method of claim 22 wherein introducing a therapeutically [offensive] effective amount further comprises administering 1-4 x 10^6 dopaminergic neurons, wherein administering further comprises loading said cells into a syringe and injecting them within the parenchyma of the patient's brain.

24. (AMENDED) An assay for [a substance] evaluating the effect of substances on differentiated neuronal cells, comprising:

A. culturing differentiated neuronal cells, said step of culturing comprising:

i. proliferating neuronal precursor cells, said step of proliferating comprising:

a. incubating said neuronal precursor cells in proliferating medium which includes basic fibroblast growth factor (bFGF); and

ii. differentiating said neuronal precursor cells, said step of differentiating comprising:

aa. incubating said precursor cells in an incubation vessel which contains differentiation medium in a manner effective to form a reaggregation of differentiated cells that is not adhered to any surface of the incubation vessel, wherein said differentiating medium includes ascorbic acid,

B. exposing said differentiated neuronal cells to the substance; and

C. observing the effect of the substance on said differentiated neuronal cells.

Claims 25-27 are new.

25. (NEW) The method of claim 1, wherein the precursor cells are obtained during a sensitive period.

26. (NEW) The method of claim 25, wherein the precursor cells comprise human fetal cells obtained between about embryonic week 5 and about embryonic week 8.

27. (NEW) The method of claim 25, wherein the precursor cells further comprise rat fetal cells obtained between about embryonic day 10 and about embryonic day 12.